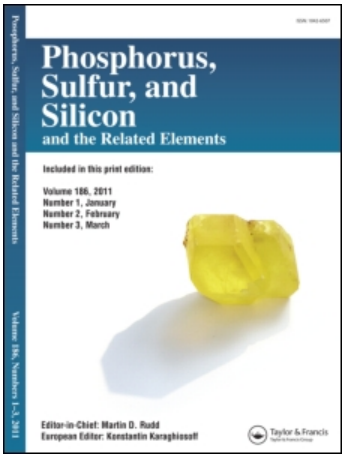

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ENANTIOSPECIFIC SYNTHESIS OF PENTACOORDINATED PHOSPHORUS COMPOUNDS X-RAYS DIFFRACTION STRUCTURE AND REACTION MECHANISM

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ENANTIOSPECIFIC SYNTHESIS OF PENTACOORDINATED PHOSPHORUS COMPOUNDS X-RAYS DIFFRACTION STRUCTURE AND REACTION MECHANISM

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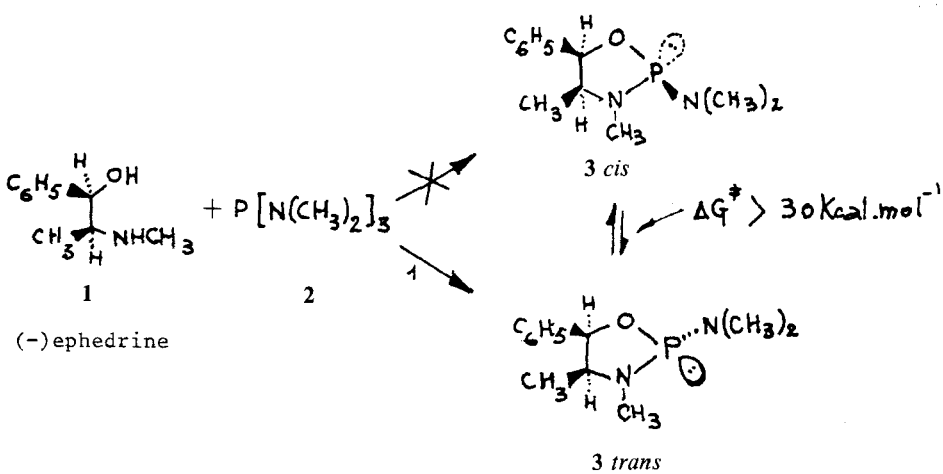
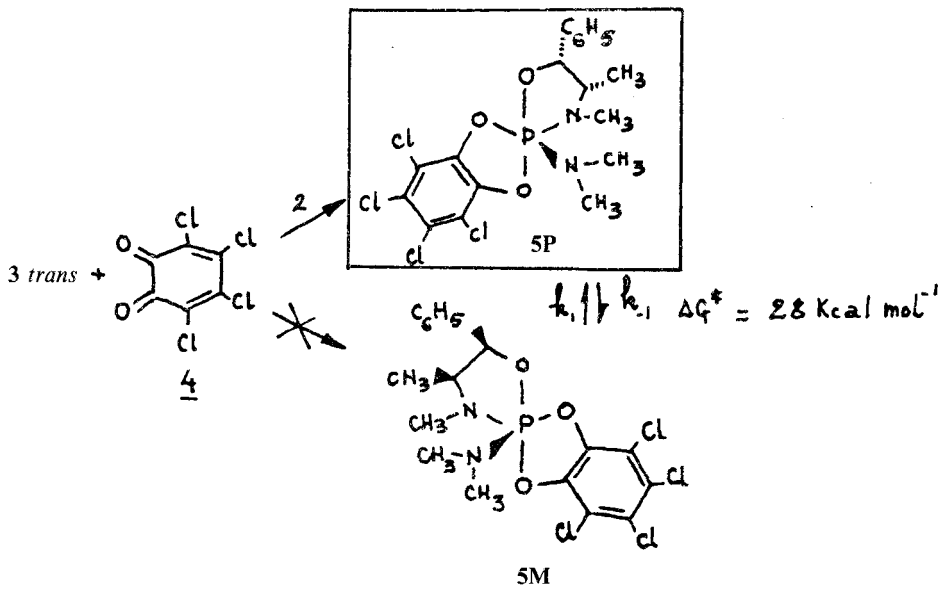
It is shown that the synthesis of the optically active spirophosphorane **5** is enantiospecific. The structure and the configuration of the enantiomeric pure diastereoisomer, given by the reaction, has been established by X-rays diffraction. A mechanism accounting for the stereospecificity is proposed. The same selectivity has been observed for three other compounds.

The optically active spirophosphorane **5**, which structure is reported in this paper, belongs to a noteworthy serie for the stereochemistry of their synthesis. This compound has been prepared by a two steps reaction (Schemes 1 and 2). The step 1 (Scheme 1): reaction between tris dimethylaminophosphine and (−) ephedrine (1R, 2S), should lead to two diastereoisomers **3** *cis* and **3** *trans*, each of them enantiomerically pure. The ^{1}H and ^{31}P N.M.R. spectroscopy shows that only one diastereoisomer is formed through step 1.[1] To rule out the eventuality of a second order asymmetric transformation during crystallization, we made sure that, by warming in benzene, the inversion barrier for **3** is higher than 30 kcal mol^{-1}. Reaction 1 is really enantiospecific.



SCHEME 1



SCHEME 2

What is the configuration of phosphorus in **3**? We can collect some converging arguments for **3** *trans* (2R), based on relative position of substituents for related cycles:

a) a detailed study of coupling constants (^{1}H N.M.R.) of **3** by J. Devillers[1c] is in favor of this configuration.

b) the 1,3 interaction of substituents $N(CH_3)_2$, C_6H_5 and CH_3 makes it plausible the destabilization of stereoisomer **3** *cis* (2S). It is the case for **6** obtained alone by a reaction close to Reaction 1 (Scheme 1) and for which the X-rays structure is known:[2] the substituents of the cycle and of phosphorus atom are *trans*.

c) the X-rays structure of compound **7**, derived from (+) ephedrine, shows, after the authors,[3] that it is the extracyclic bulkiest atom linked to phosphorus—here sulfur—which is *trans* with respect to the ring substituents.

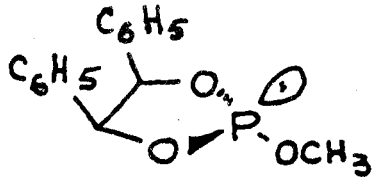
The cyclization on a carbon atom offers also some arguments:

d) cyclization of (−) ephedrine with benzaldehyde leads to the "*trans*" oxazolidine **8**.[4]

e) cyclization of (−) ephedrine with acetylenedicarboxylic methylester yields stereospecifically the oxazolidine **9**. The X-rays structure shows, according to the authors, the bulkiest substituents in *trans* position.[5]

These arguments strongly suggest that reaction 1 (Scheme 1) leads to **3** *trans* (2R).

Condensation of orthoquinone **4** with **3** *trans* (reaction 2, Scheme 2) leads to the spirophosphorane **5**. The N.M.R. spectroscopy shows that this synthesis gives only one diastereoisomer. Compound **5** can exist as two diastereoisomers **5M** and **5P** (Scheme 2), epimers at the level of the phosphorus atom. In other respects, we know that these two diastereoisomers can interconvert one in the other by intramo-



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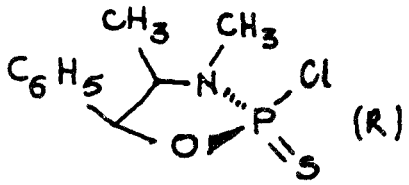

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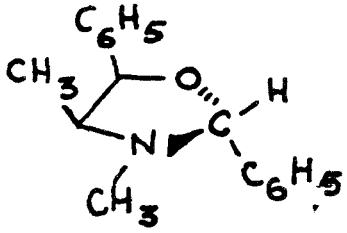

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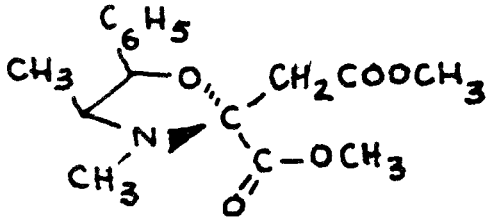


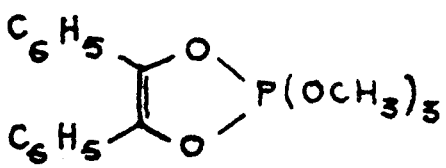
9

lecular isomerization,[6] leading to an equilibrium between the two forms; now the reaction 2 (Scheme 2), in benzene, at room temperature, gives only one form! The explanation of this observation lays in the kinetic determination of the isomerization barrier of **5M** $\rightleftharpoons$ **5P**. We found $\Delta G^{\neq} = 27.95$ kcal mol^{-1} in C_6H_6 at 80°C ($t_{1/2} =$ 300 min, $k_1 = 2.26\ 10^{-5}s^{-1}$, $k_{-1} = 1.57\ 10^{-5}s^{-1}$ at 80°C). This barrier, the highest found for spirophosphoranes,[7] involves that the synthesis of **5**, through reaction 2 (Scheme 2) is enantiospecific.

Ogata *et al.*[8] had shown, on related systems, that the first step of the reaction, which is the slow one, is the attack of **3** upon **4** by the lone pair of the phosphorus atom. These authors did not bring any stereochemical arguments because the final product was an achiral phosphorane: **10**. The determination of the configuration about phosphorus of the isomer of **5** obtained by synthesis is of interest for this mechanism because it provides a conclusive information on the stereochemical course of the reaction.

The X-rays analysis was conducted under the following experimental conditions: space group $P2_1$, monoclinic, $a = 15.37_2$, $b = 7.02_8$, $c = 0.95_5$ Å; $\beta = 94.53°$, measured with the K_α copper radiation ($\lambda = 1.54178$ Å). Residual factor: 0.046 for 1850 reflexions. For the absolute structure 80% probability after the Hamilton test.[9]

The main results are: compound **5**, given by the synthesis, is a slightly distorted T.B.P. (18% deformation rate according to the MUETTERTIES criterium[10]) with *a right handed helicity* (see O.R.T.E.P. drawing Figure 1), the O_2PO_3 angle is 171.29°(0.29).[11]



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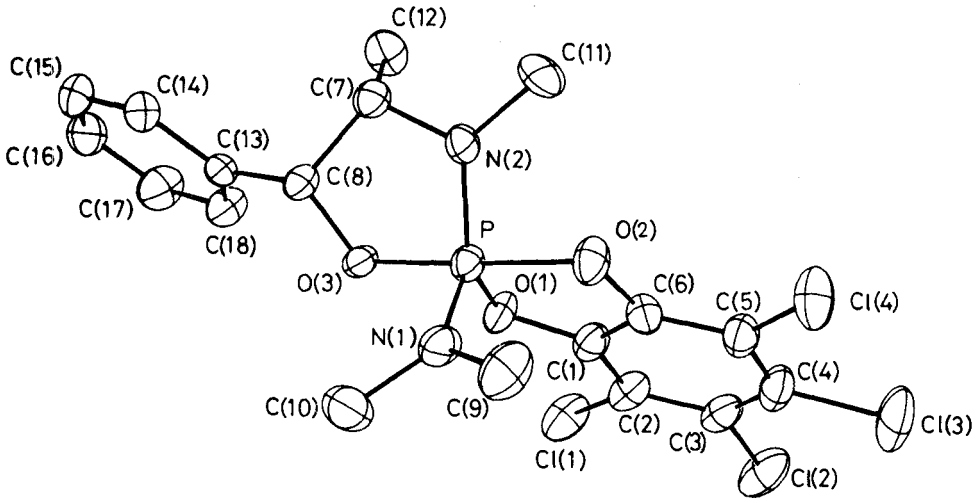
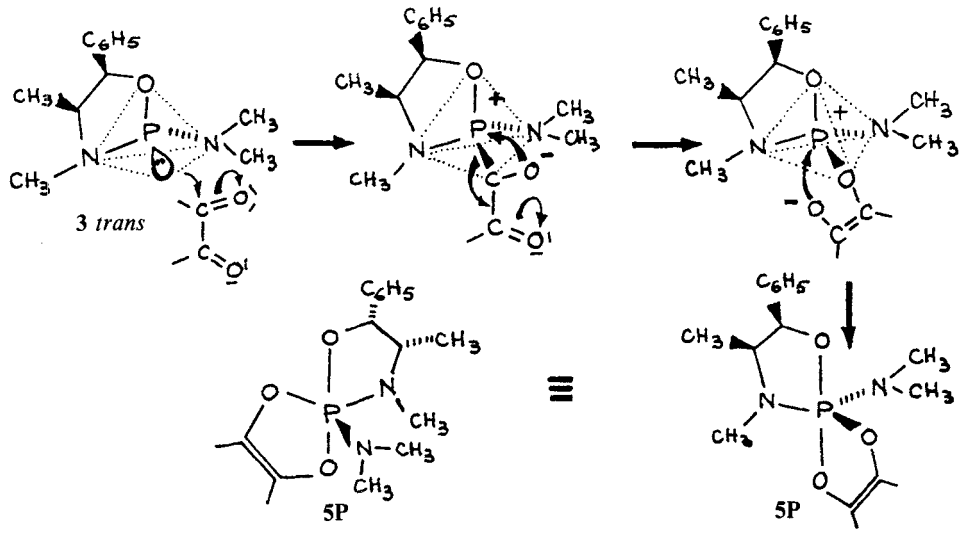


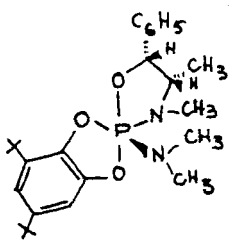
FIGURE 1

The synthesis of **5**, by reaction 2 (Scheme 2) which was conducted at room temperature in benzene, allowed us, taking into account the barrier of epimerization of **3** and **5**, to rule out any "thermodynamic control": this reaction is "kinetically controlled" in other words it depends on the relative energy of the transition states and we shall specify this point later.

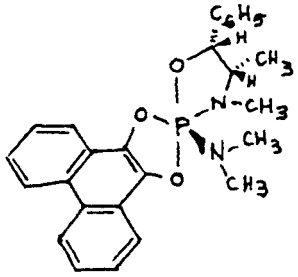
The mechanism[8] put forward for a reaction leading to compounds close to **5**, can be transposed for reaction **2**: Scheme 3. The first step, the slower, is the attack of the lone pair of the phosphorus atom on a carbonyl carbon followed by a fast three centers rearrangement which gives a tetracoordinated phosphorus zwitterion with



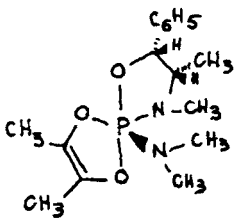
SCHEME 3



11P



12P



13P

the same configuration as that of the starting product. In the last step the oxanion attacks the tetracoordinated phosphonium by such a face of the tetrahedron that the ephedrinic oxygen and the entering one will hold the two apical positions of the pentacoordinated specie (the two nitrogen atoms lay in equatorial positions): that is admitted as general rule for this type of reaction.[12] The helicity of the obtained spirophosphorane is consequently directly dependent of the configuration about phosphorus in the starting P^{III}, in other words, of the height of the isomerization barrier of the starting P^{III}.

This stereochemical path is consistent with the relative configuration of the starting P^{III}: **3** *trans* and the formed P^{V}: **5P**, the $N(CH_3)_2$ substituent on phosphorus and the substituents on the cycle derived from (−) ephedrine (CH_3 and C_6H_5) are *trans* in the two species.

This mechanism can be considered as general for this type of reaction: we observed an identical stereospecificity for analogous compounds. The condensation of ditertiobutyl quinone, phenanthren quinone and 2,3-butanedione yields respectively **11P**, **12P** and **13P** with the same configuration at the level of the phosphorus than **5P**. These configurations have been determined by ^{1}H N.M.R. spectroscopy correlations.[6] These compounds show, as for **5**, a barrier of epimerization higher than 27 kcal mol^{-1}. For instance the barrier for **13** is 28.34 kcal mol^{-1}, $k_{app} = 0.84\ 10^{-5} s^{-1}$ at 72.4°C. The barrier of epimerization for **11** and **13** is too high to be measured without decomposition. These facts are in agreement with the same mechanism of condensation as for **5** and are self-consistent with the Ogata's one.[8]

EXPERIMENTAL

100 MHz ^{1}H N.M.R. spectra were taken with a Varian HA 100 instrument for C_6D_6 solutions with tetramethylsilane as internal standard; 24.3 MHz ^{31}P N.M.R. with a Perkin-Elmer R 10 with 85% H_3PO_4 as internal standard.

The rates of epimerization of **5** and **13** were obtained from the linear plot of $Ln(G_t - G_\infty)$ against time where G_t is the optical rotation of the solution at time t or the intensity of a suitable ^{1}H N.M.R. signal, G_∞ is the optical rotation or the same ^{1}H N.M.R. signal after more than ten times $t_{1/2}$.

The optical rotations were taken with a Perkin-Elmer 141 instrument to within 0,002° in a temperature controlled cell (±0,05°C). The kinetic parameters were calculated using LSG program[13] processed on an Iris 80 computer or the same program adapted to a Tektronix 4051 computer equipped with a graphic system. For the evaluation of the error one can see a previous paper.[14]

Dimethylamino-5 dimethyl-8,9 phenyl-7 tetrachlorobenzo-2,3 trioxa-1,4,6 aza-9 phospha(V)-5 spiro[4,4]-nonane (7R) (8S). **5**

Dimethylamino-2 dimethyl-3,4 phenyl-5 oxazaphospholane-1,3,2 (4R) (5S) **3** (0,01 mole) (derived from (−) ephedrine) in benzene (10 ml) magnetically stirred reacts with a dropwise added (4 hours) solution of tetrachloroorthoquinone (0,01 mole) in benzene (10 ml) at room temperature. The reaction is well fol-

lowed by the disappearance of the deep red color of o.quinone solution. The phosphorane is purified by filtration on alumina. M.P.: 160 ± 2°C (calc. for $C_{18}H_{19}N_2O_3Cl_4P$: C, 44.63; H, 3.92; N, 5.78; P, 6.40. Found: C, 44,93; H, 4.32; N, 6.40; P, 6.83).

RMN ^{31}P (C_6D_6) δ: −34
RMN ^{1}H (C_6D_6)

Diastereoisomer obtained by synthesis

4,75 (1H, d. $^3J_{HCCH}$ = 5,7 Hz *H*—C(C$_6$H$_5$)O); 2,44 (6H, d, $^3J_{HCNP}$ = 11 Hz, (*Me*)$_2$—N—); 2,65 (3H, d, $^3J_{HCNP}$ = 12,7 Hz, *Me*—N<); 0,49 (3H, d, $^3J_{HCCH}$ = 6 Hz, *Me*—C—)

Second diastereoisomer

5,07 (1H, d, $^3J_{HCCH}$ = 5,5 Hz *H*—C(C$_6$H$_5$)O); 2,55 (6H, d, $^3J_{HCNP}$ = 14 Hz, (*Me*)$_2$—N—); 2,53 (3H, d, $^3J_{HCNP}$ = 9,1 Hz, *Me*—N<); 0,43 (3H, d, $^3J_{HCCH}$ = 5,8 Hz, *Me*—C—)

Dimethylamino-5 (benzoditertiobutyl-3',5')-2,3 dimethyl-8,9 phenyl-7 trioxa-1,4,6 aza-9 phospha(V)-5 spiro[4,4]nonane (7R) (8S) **11**

Prepared as **5** (calculated for $C_{26}H_{39}N_2O_3P$: C, 68.12; H, 8.51; N, 6.11; P, 6.76. Found: C, 68.29; H, 8.70; N, 5.93; P, 6.75)

RMN ^{31}P: (C_6D_6) δ = −38
RMN ^{1}H: (C_6D_6)

Owing to the two possibilities of plugging the benzogroup on TBP, there exists a pair of diastereoisomers for each helix, hence four different structures. Consequently each signal is splitted.

Diastereoisomers obtained by synthesis

4,99 (1H, d, $^3J_{HCCH}$ = 6 Hz *H*—C(C$_6$H$_5$)O); 4,98 (1H, d, $^3J_{HCCH}$ = 6 Hz, *H*—C(C$_6$H$_5$)O) 2,80 (3H, d, $^3J_{HCNP}$ = 9 Hz, *CH*$_3$—N<); 2,88 (3H, d, $^3J_{HCNP}$ = 9 Hz, *CH*$_3$—N<) 2,67 (6H, d, $^3J_{HCNP}$ = 11 Hz, (*CH*$_3$)$_2$—N—); 2,66 (6H, d, $^3J_{HCNP}$ = 10,5 Hz, (*CH*$_3$)$_2$—N—) 0,69 (3H, d, $^3J_{HCCH}$ = 7 Hz, *CH*$_3$—C—); 0,68 (3H, d, $^3J_{HCCH}$ = 7 Hz, *CH*$_3$—C—)

Second pair of diastereoisomers

5,45 (1H, d, $^3J_{HCCH}$ = 5,5 HZ *H*—C(C$_6$H$_5$)O); 5,36 (1H, d, $^3J_{HCCH}$ = 5,5 Hz; *H*—C(C$_6$H$_5$)O); 2,68 (3H, d, $^3J_{HCNP}$ = 9,4 Hz, *CH*$_3$—N<); 2,70 (3H, d, $^3J_{HCNP}$ = 9 Hz, *CH*$_3$—N<) 2,80 (6H, d, $^3J_{HCNP}$ = 10,2 Hz, (*CH*$_3$)$_2$—N—); 2,75 (6H, d, $^3J_{HCNP}$ = 10,4 Hz, (*CH*$_3$)$_2$—N—); 0,66 (3H, d, $^3J_{HCCH}$ = 6,2 Hz, *CH*$_3$—C—); 0,66 (3H, d, $^3J_{HCCH}$ = 6,2 Hz, *CH*$_3$—C—)

Dimethylamino-5 dimethyl-8,9 phenyl-7 (phenanthrenyliden-1'-2') 2,3 trioxa-1,4,6 aza-9 phospha(V)-5 spiro[4,4]nonane (7R) (8S) **12**

Prepared as **5**. The reaction mixture is heated at 60°C on account of the slight solubility of the 1,2-phenanthren quinone in benzene at room temperature M.P.: 85°C. (Calculated for $C_{26}H_{27}N_2O_3P$: C, 69.95; H, 6.05; N, 6.28; P, 6.95. Found: C, 68,81; H, 6.15; N, 6.20; P, 7.61)

RMN ^{31}P: (C_6D_6) $\delta = -35$
RMN ^{1}H: (C_6D_6)

Diastereoisomer prevalent after synthesis (80%)

5,05 (1H, d, $^3J_{HCCH} = 5,8$Hz, H—$\underset{|}{C}(C_6H_5)O$); 2,66 (6H, d, $^3J_{HCNP} = 10,8$ Hz, $(Me)_2$—N—); 2,88 (3H, d, $^3J_{HCNP} = 9,5$ Hz, Me—N$<$); 0,68 (3H, d, $^3J_{HCCH} = 6,4$ Hz, Me—$\underset{|}{C}$—)

Second diastereoisomer (20%)

5,39 (1H, d, $^3J_{HCCH} = 5,4$ Hz, H—$\underset{|}{C}(C_6H_5)O$); 2,81 (6H, d, $^3J_{HCNP} = 10,7$ Hz, $(Me)_2$—N—); 2,74 (3H, d, $^3J_{HCNP} = 9,7$ Hz), Me—N); 0,66 (3H, d, $^3J_{HCCH} = 6,3$ Hz, Me—$\underset{|}{C}$—)

Dimethylamino-5 tetramethyl-2,3,8,9 phenyl-7 Δ-2 trioxa-1,4,6 aza-9 phospha(V)-5 spirononane[4,4] (7R) (8S) **13** as described in Ref. 15.

The product is crystallized in hexane (calculated for $C_{16}H_{25}N_2O_3P$: C, 59.26; H, 7.71; N, 8.64; P, 9.56. Found: C, 59.13; H, 7.75; N, 8.60; P, 9.61). RMN ^{1}H: (C_6D_6)

Diastereoisomer obtained by synthesis

4,99 (1H, d, $^3J_{HCCH} = 5,6$ Hz, H—$\underset{|}{C}(C_6H_5)O$); 2,75 (6H, d, $^3J_{HCNP} = 10,4$ Hz, $(Me)_2$—N—); 2,86 (3H, d, $^3J_{HCNP} = 8,9$ Hz, Me—N$<$); 0,72 (3H, d, $^3J_{HCCH} = 5,5$ Hz, Me—$\underset{|}{C}$— ephedrine)

Second diastereoisomer

5,33 (1H, d, $^3J_{HCCH} = 5,4$ Hz, H—$\underset{|}{C}(C_6H_5)O$); 2,87 (6H, d, $^3J_{HCNP} = 10,3$ Hz, $(Me)_2$—N—); 2,78 (3H, d, $^3J_{HCNP} = 9,3$ Hz, Me—N$<$); 0,66 (3H, d, $^3J_{HCCH} = 6.4$ Hz, Me—$\underset{|}{C}$— ephedrine)

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